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09/010377

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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EXAMINER

HM12/0104

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ART UNIT	PAPER NUMBER
1644	9

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 10/19/99

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-17 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-17 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

* U.S. GPO: 1995-404-438/40517

DETAILED ACTION

1. Applicant's election without traverse of herpes virus in Paper No. 8 is acknowledged

2. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.
Applicant is reminded to indicate Figures 3A, 3B and 3C in the Brief Description of the Drawings.

3. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

For example, page 16, line 7; "encephalitis" should be "encephalitis".

Applicant is required to identify the nucleotide and amino acid sequences in the specification with SEQ. ID NOS.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-8, 11, and 14-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating viral encephalitis with "antibodies that bind the alpha-4 subunit of VLA-4", does not reasonably provide enablement for any "agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin". The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies such "agents" other than those encompassed by the VLA-4α-specific antibodies. While agents" "that inhibit binding of leukocytes to brain endothelial cells" or "that specifically bind the alpha-4 subunit of VLA-4", may have some notion of the activity of the "agents", claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make and use such "agents", commensurate in scope with the claimed invention.

It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different pharmacological activities. Applicant has not enabled structurally related nor unrelated compounds comprising "any agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin" or "any agent that specifically bind the alpha-4 subunit of VLA-4". Such structurally unrelated compounds/agents would be expected to have greater differences in their activities. There is insufficient direction or objective evidence as to how to make and to how to use any agent that "inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin" or "that specifically bind the alpha-4 subunit of VLA-4", for the number of possibilities associated with the myriad of direct and indirect effects associated with various adhesion pathways or molecules and, in turn, as to whether such a desired effect can be achieved or predicted, as encompassed by the claims.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the in vivo experimental models of BDV-infected rats accurately reflects the relative efficacy of any agent "any agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin"or "that specifically bind the alpha-4 subunit of VLA-4", which can treat viral encephalitis.

In addressing adhesion-based therapy, Harlan states that whether you go humanized antibody, peptide, soluble receptor, or saccharide; it's still a long way to product (Edgington, Biotechnology, 1992; see entire document, particularly page 386, column 3, paragraph 4). The inherent difficulties of this approach include development of serum sickness after injection of foreign protein, diminishing therapeutic effects after prolonged therapy and the potential for promotion of infection.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the changes which can be made in the structure of "any agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin"or "that specifically bind the alpha-4 subunit of VLA-4", and still provide or maintain sufficient activity to treat viral encephalitis would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

6. Claim 13: It is apparent that the 21.6 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line / hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

Applicant is reminded that the following and should amend the specification accordingly.
The current address of the ATCC is as follows:
American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

It is noted that the sequence of an entire immunoglobulin satisfies the biological deposit of said 21.6 immunoglobulin. Note that satisfaction for the biological deposit of the specific 21.6 antibody requires the disclosure and recitation of its entire amino acid sequence and not based upon partial sequences.

7. Claim 13 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

. Claim 13 is indefinite in the recitation of "21.6" because its characteristics are not known. The use of "21.6" monoclonal antibody as the sole means of identifying the claimed antibody renders the claim indefinite because "21.6" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation s to define completely distinct antibodies/hybridomas or other cell lines.

Further this claim is indefinite in its recitation because it is unclear whether the recitation of "characterized by ... SEQ ID NO:2" refers back to the 21.6 antibody itself or to the humanized antibody of 21.6 antibody

Applicant should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-13, 15-16 are rejected under 35 U.S.C. § 102(e) as being anticipated by Bendig et al. (U.S. Patent No. 5,840,299, as evidenced by Sanders et al. (Archives of Neurology 53: 125-133, 1996) AND/OR Editorial (Archives of Neurology, 53: 123-124, 1996) AND/OR Soilu-Hanninen et al. (J. Neuroimmunol. 72: 95-105; 1449)..

Bendig et al. teach using VLA-4α-specific antibodies, including the 21.6 specificity to treat encephalitis (see entire document, including VII. Methods of Treatment on columns 14-16) treating encephalitis and multiple sclerosis). Bendig et al. Differs from the claimed methods by not disclosing a viral source of encephalitis or treating patients prophylactically.

Both Archives of Neurology citations disclosed that herpes is a common neurotropic virus which was present in more multiple sclerosis patients than control cases (see entire documents).

Soilu-Hanninen et al teach that viral infections serve as triggers of relapse phases of multiple sclerosis (see entire document, including the Abstract, Introduction and Discussion).

Therefore, treating multiple sclerosis patients with VLA-4α-specific antibodies, which was also taught for treating encephalitis would have had the inherent property of prophylactically treating encephalitis due viral infections, including herpes virus in such multiple sclerosis patients. Such patients are treated with standard antiinflammatory agents and monitored for encephalitis. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods of treating multiple sclerosis patients with VLA-4α-specific antibodies.

Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999). ; Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

11. Claims 1, 2, 4, 6-9 and 16 are rejected under 35 U.S.C. § 102(b) as being anticipated by Soilu-Hanninen et al. (Scand. J. Immunol. 43: 727, 1996) (see Abstract).

Soilu-Hanninen et al. teach using VLA-4α-specific antibodies to treat virus-facilitated EAE including by arboviruses.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods of treating multiple sclerosis patients with VLA-4α-specific antibodies.

Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999).; Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

12. Claims 1, 2, 4, 6-9 and 16 are rejected under 35 U.S.C. § 102(a)(b) as being anticipated by Soilu-Hanninen et al. (J. Neuroimmunol. 72: 95-105; 1997; 1449) (see entire document)..

Due to the ambiguity of the public availability of this document, this rejection is made under 35 U.S.C. § 102(a) or (b).

Soilu-Hanninen et al. teach using VLA-4α-specific antibodies to treat virus-facilitated EAE, including its implications relapses triggered by viral infections in multiple sclerosis and by arboviruses (see entire document, including the Abstract, Introduction and Discussion).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods of treating multiple sclerosis patients with VLA-4α-specific antibodies.

Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999).; Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

13. Claims 1-17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bendig et al. (U.S. Patent No. 5,840,299) AND/OR Soilu-Hanninen et al. (Scand. J. Immunol. 43: 727, 1996) AND/OR Soilu-Hanninen et al. (J. Neuroimmunol. 72: 95-105; 1997; 1449).

Bendig et al. teach using VLA-4α-specific antibodies, including the 21.6 specificity to treat encephalitis (see entire document, including VII. Methods of Treatment on columns 14-16) treating encephalitis and multiple sclerosis). Bendig et al. differs from the claimed methods by not disclosing a viral source of encephalitis or treating patients prophylactically.

Soilu-Hanninen et al. teach using VLA-4α-specific antibodies to treat virus-facilitated EAE, including its implications relapses triggered by viral infections in multiple sclerosis and by arboviruses (see entire documents). Soilu-Hanninen et al teach that viral infections serve as triggers of relapse phases of multiple sclerosis and the relationship of viral infection with the facilitation of leukocyte entry into the CNS (see entire document, including the Abstract, Introduction and Discussion, 1997).

The primary references differ from the claimed methods by not referring to the symptomatic/asymptomatic symptoms or pediatric nature of the patients or monitoring the patients for encephalitis or providing antiviral/anti-inflammatory agents in addition per se.

However, given the clear teaching of treating encephalitis and multiple sclerosis with VLA-4α-specific antibodies, as well as the teaching that viral infections can serve as triggers of relapse phases of multiple sclerosis; treating patients populations encompassing symptomatic, asymptomatic and pediatric patients would have been targeted by the ordinary artisan at the time the invention was made. Also, given the viral component of multiple sclerosis; the ordinary artisan would have provide standard antiinflammatory and antiviral treatment in addition to t VLA-4α-specific antibodies at the time the invention was made.

One of ordinary skill in the art at the time the invention was made would have been motivated to select VLA-4α-specific antibodies to treat viral encephalitis; given the ability of these VLA-4α-specific antibodies to treat both multiple sclerosis and encephalitis and the known role of viruses in inducing encephalitis at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claims 1-17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bendig et al. (U.S. Patent No. 5,840,299) AND/OR Soilu-Hanninen et al. (Scand. J. Immunol. 43: 727, 1996) AND/OR Soilu-Hanninen et al. (J. Neuroimmunol. 72: 95-105; 1997; 1449), as applied to claims above and in further view of the art known role or etiology of various viruses inducing encephalitis, as evidenced by Planz et al. (J. Virol. 69: 896-903, 1995; 1449)
AND/OR
the role herpesviruses in multiple sclerosis, as taught by Sanders et al. (Archives of Neurology 53: 125-133, 1996) AND/OR Editorial (Archives of Neurology, 53: 123-124, 1996)

Bendig et al., Soilu-Hanninen et al. Soilu-Hanninen et al. Are taught above and differ from the claimed methods by not disclosing other known viruses contributing to either encephalitis or multiple sclerosis.

Planz et al. Teach the role of T cell subsets in borna disease virus induce progressive encephalitis (see entire document).

Both Archives of Neurology citations disclosed that herpes is a common neurotropic virus which was present in more multiple sclerosis patients than control cases (see entire documents).

Given the clear teaching of treating encephalitis and/or multiple sclerosis with VLA-4α-specific antibodies, as well as the teaching that viral infections can serve as triggers of relapse phases of multiple sclerosis as taught by Soilu-Hanninen et al. Or that viral infections can lead to encephalitis as taught by Planz et al. Or that herpesviruses are associated with multiple sclerosis; treating patients populations encompassing symptomatic, asymptomatic and pediatric patients would have been targeted by the ordinary artisan at the time the invention was made. Also, given the viral component of encephalitis sclerosis; the ordinary artisan would have provide standard antiinflammatory and antiviral treatment in addition to t VLA-4α-specific antibodies at the time the invention was made.

One of ordinary skill in the art at the time the invention was made would have been motivated to select VLA-4α-specific antibodies to treat viral encephalitis; given the ability of these VLA-4α-specific antibodies to treat both multiple sclerosis as well as encephalitis and the known role of viruses in inducing encephalitis at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Patent Examiner
Technology Center 1600
December 29, 1999
PHILLIP GAMBEL